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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/688,851	10/16/2000	Jeffrey M. Staub	15868/02	1808

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1638

DATE MAILED: 03/12/2003

*LJ*

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	09/688,851	STAUB ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	Georgia L. Helmer	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

**A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM  
 THE MAILING DATE OF THIS COMMUNICATION.**

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) Responsive to communication(s) filed on 12 December 2002.
- 2a) This action is **FINAL**.      2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) Claim(s) 24-26,28 and 32 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) Claim(s) \_\_\_\_\_ is/are allowed.
- 6) Claim(s) 24-26,28 and 32 is/are rejected.
- 7) Claim(s) \_\_\_\_\_ is/are objected to.
- 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on 12 December 2002 is/are: a) accepted or b) objected to by the Examiner.  
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) The proposed drawing correction filed on \_\_\_\_\_ is: a) approved b) disapproved by the Examiner.  
 If approved, corrected drawings are required in reply to this Office action.
- 12) The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some \* c) None of:  
 1. Certified copies of the priority documents have been received.  
 2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).  
 a) The translation of the foreign language provisional application has been received.
- 15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- |  |  |
|--|--|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                    | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ . |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)           | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)  |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ . | 6) <input type="checkbox"/> Other: _____ .                                   |

***Status of the Claims***

1. The Office acknowledges receipt of Applicants Response; dated 12 December 2002, Paper No. 20.
2. Applicant has amended claims 24, 25, 26 28, and 32, and cancelled claims 27 and 29-31. Claims 24, 25, 26, 28, and 32 are pending, and are examined in the instant action.
3. All rejections not addressed below have been withdrawn.
4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

***Drawings***

5. The Office acknowledges receipt of Formal Drawings, Paper No. 21, filed 12 December 2002.

***Claim Rejections - 35 USC § 112-second***

6. Claims 24, 25, 26, 28, and 32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 24, 25, 26, 28, and 32 are incomplete method claims, because the final step of the method does not result in the production of the desired product recited in the preamble.

Claims 24, 25, 26, 28, and 32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 24, 25, 26, 28, and 32 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps in claim 24 are:

- Producing a plastid having the first recombinant DNA sequence in the plant cell (line 7),
- Producing excision of said selectable marker (line 9),
- Thereby producing a plastid having the second recombinant DNA sequence in a plant cell of said transplastomic plant, (line 15)
- Producing a transplastomic plant having two recombinant DNA sequences introduced sequentially into the plastid using the same selectable marker for the second DNA as used for the selection of the first recombinant DNA (last line).

In claim 24

- "gene" is unclear because a "gene" implies a DNA sequence that exists in nature and includes coding and noncoding regions, as well as all regulatory sequences associated with expression. Since this does not appear to be Applicant's intention, the language "a DNA sequence of interest" is suggested. Or Applicant may recite the various components of

the "gene" desired. All subsequent recitations of this language are also rejected.

Correction and/or clarification are required.

***Claim Rejections - 35 USC § 112***

7. Claims 24, 25, 26, 28, and 32 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant claims a method for performing "a plurality of separate transformations"; which is new matter and is not supported by the specification as originally filed.

***Claim Rejections - 35 USC § 112-1<sup>st</sup>, enablement***

8. Claims 24, 25, 26, and 32 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection is maintained as applicable to the *recombinant sites*.

Re the recombinant sites. . The only way the invention can work to excise intervening DNA is for the identical recombinant sites to be positioned in parallel, as

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direct repeats, flanking the DNA to be excised (Odell et al; 1994. In J Paszkowski, ed, Homologous Recombination in Plants. Kluewer Academic Publishers, Dordrecht, The Netherlands, pps 219-270. See p225 and 239).

Applicant teaches in Example 4 tobacco cells having transformed chloroplasts containing a GFP gene disrupted with an antibiotic resistance marker flanked by direct repeats of lox recombining sites. Upon exposure of this DNA to Cre recombinase, the marker was excised and function of the GFP restored. Applicant does not teach how to excise a target nucleotide sequence wherein said target sequence is flanked by recombining sites, wherein the recombining sites are in any orientation other than in direct repeat orientation.

It is known that multiple molecular reactions can occur in the presence of recombinases and their recombining sites. (See Kilby, et al, 1993, Trends in Genetics 9: 413-421, especially page 417, Figure 4 (b)). Lox recombining sites flanking a nucleotide sequence will function to excise that nucleotide sequence only if the lox recombining sites are in direct repeat orientation with respect to each other. The DNA sequence of the lox sites is asymmetric and has directionality; the lox sites can only align successfully in one orientation (Kilby, 1993, page 416, Figure 3 (b)). It is unpredictable that any configuration other than the direct repeat orientation of the lox sites will function to excise the flanked a nucleotide sequence. No guidance is given for how to excise the intervening DNA sequence with any other configuration of the lox recombining sites. Applicant has provided no guidance on how to predictably eliminate

inoperable embodiments from a virtually ad infinitum of possibilities other than by random trial and error, which is excessive experimentation and an undue burden.

In view of the breadth of the claims (any plant cell and any plastid, any of three recombinase systems-Cre, FLP and R, and any selectable marker), the lack of guidance in the specification, the lack of working examples, undue experimentation would be required to enable the invention as commensurate in scope with the claims.

***Claim Rejections - 35 USC § 103***

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

10. Claims 24, 25, 26, 28, and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dale, et al, (Proc. Natl. Acad. Sci. USA, Vol 88, pages 10558-10562, 1991), in view of Svab, et al, (Proc. Natl. Acad. Sci. USA, Vol 90, pages 913-917, 1993).

Dale teaches a method for performing a plurality of separate transformations in a plant cell using the same selectable marker gene for selection of transgenic plants, comprising introducing into a plant cell a first recombinant DNA sequence comprising a construct capable of being integrated in the genome of the plant cell, said construct comprising a DNA sequence encoding a selectable marker gene flanked by a pair of

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compatible recombining sites (Abstract; Figure 1, pg 10559), providing a recombinase (p 10559, last full paragraph), regenerating a transgenic plant (p 10560, 1<sup>st</sup> column) containing the first recombinant DNA sequence without said selectable marker gene, introducing a second recombinant DNA sequence comprising a construct capable of being integrated into the genome of the plant cell, said construct comprising a second DNA sequence encoding said selectable marker gene into the plant cell of the transgenic plant obtained from the regenerated plant (Abstract, last line). Dale also teaches a recombinase provided to plant cells by a third recombinant DNA sequence (p 10559, last full paragraph), a gene other than a selectable marker gene outside of the pair of recombining sites (Figure 2, p 10560), recombining sites in directly repeated orientation (Figure 1, p 10559), and Lox recombining sites. Dale teaches a method of gene transfer that does not leave behind a selective marker.

Dale does not teach plastid transformation.

Svab teaches plastid transformation, and the production of high frequency plastid transformation by selection for a selectable marker gene (Abstract and last full paragraph, p 913). It would have been obvious to one of skill in the art, at the time of the invention was made, to substitute for the transgenes of Dale, the plant cell plastid genes of Svab, and to use the invention to produce transplastomic plants

Given the recognition of one of ordinary skill in the art of the value of a method of gene transfer that does not leave behind a selectable marker in the host genome, and the fact that plastid transformation is desirable as evidenced by Svab, one of ordinary skill in the art would have been motivated to transform plastids by using the same

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selectable marker on subsequent rounds of transformation into the same host as taught by Dale, to routinely transform plastids without leaving a marker gene behind, and to be able to use the same selective marker sequentially over generations of plastid transformations, with a reasonable expectation of success.

Thus the claimed invention would have been *prima facie* obvious as a whole to one of ordinary skill in the art at the time it was made. Accordingly, the claimed invention is *prima facie* obvious in view of the prior art.

#### REMARKS

11. No claims are allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Georgia L. Helmer whose telephone number is 703-308-7023. The examiner can normally be reached on 8:30 - 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on 703-306-3218. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Georgia L. Helmer  
Patent Examiner  
Art Unit 1638  
February 24, 2008

  
PHUONG T. BUI  
PRIMARY EXAMINER 2/24/03